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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/642,609	08/17/2000	Yoshinari Kumagai	BEAR-004	6929

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EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,609	KUMAGAI ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT OF AMENDMENT, REMARKS, STATUS OF THE APPLICATION AND CLAIMS

1. The amendment and remarks filed 10/1703 are acknowledged, entered and considered. In view of Applicant's request claim 12 has been amended, claims 20-22 have been added and claims 1-11 and 17-19 have been withdrawn as non-elected invention. Thus, claims 1-22 are now pending in the application. The objections to the abstract and the specification and the rejection under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicant's amendment and remarks filed 7/21/03. However, the rejection under 35 U.S.C. 103(a) over the prior art of record including newly submitted claims 2-22 are maintained for the same reasons discussed in the previous Office action.

CLAIM REJECTIONS-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-16 and newly submitted claims 20-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds (U.S. Patent No. 5,015,628) in view of Monier-Faugere et al., (Cecil Textbook of Medicine, 21st Edition, Volume 2, Chapter 266, pages 1409-1414, edited by Goldman, Published by W.B. Saunders Company, 2000).

Independent claim 12 as currently amended is directed to the use of a compound which is defined as a compound characterized by a) oral bioavailability, b) 4-30 amino acid residues, and c) having at least one amino acid residue which is phosphorylated or which is phosphorylatable *in vivo* or *in vitro*. The prior art of Reynolds renders the claim obvious because it teaches a composition comprising a phosphopeptide having from 5-30 amino acids, wherein the composition is in a form of pharmaceutical composition and administered orally to a mammal in a therapeutically effective amount (See e.g., col. 1, lines 10 to col. 2, lines 8 and col. 3, lines 9-14). The reference of Reynolds on col. 2, lines 50-68 further teaches that the composition preferably comprises a peptide which is

present as 0.01 to 10% by weight which is a unit of 1 to 1000, and as such is equivalent to a composition comprising 1 to 1,000 mg of the peptide compound as claimed in claim 13 (i.e., since mg reflects weight unit). Also, the reference discloses that the peptidic compound exhibits a reduction in hydroxyapatite dissolution rate of at least 15% which meets the limitation of reduction serum phosphate levels 5% or more of claim 15 because on col. 6, lines 59-61, the reference states that the reduction in hydroxyapatite dissolution was related to phosphoserine content and spacing within a peptide.

The references of Reynolds differ from claims 12-16 and 2-22 in not teaching a method of treating hyperphosphatemia (an excess amount of phosphate in the blood) by administering orally the peptidic compound claimed and the duration time of the administration. However, the primary reference of Reynolds on col. 8, lines 27-34 states that the ability of these peptides to sequester calcium phosphate can be utilized in the treatment of various rarefying bone diseases. These peptides can significantly increase the absorption of calcium, phosphate and iron in the gut. Hence, pharmaceutical vehicles (e.g., enteric capsules) or foods containing calcium phosphate T1 and ferrous phosphate T1 can be used for the treatment of osteoporosis/osteomalacia and anemia. For support, see the secondary reference of Monier-Faugere et al., (Cecil Textbook of Medicine, 21st Edition, Volume 2, Chapter 266, pages 1409-1414, edited by Goldman, Published by W.B. Saunders Company, 2000) which teaches the association of diseases of bone and bone mineral metabolism. For example, on page 1409, the reference teaches the relationship and/or coexistence of calcium, parathyroid hormone (PTH) and phosphate in renal osteodystrophy, which

encompasses a wide variety of derangements in mineral and bone metabolism. Further, on page 1410, the reference discloses the associations and mechanisms of how hyperphosphatemia result in advanced renal failure in which the increased serum phosphorus levels and PTH further decreases serum calcium through physicochemical binding affecting the histological pattern of renal osteodystrophy resulting in a profound decrease in bone turnover, i.e., low number of active remodeling sites resulting in bone resorption and suppressed bone formation.

Furthermore, the primary reference of Reynolds suggests the treatment of various rarefying bone diseases such as osteoporosis/osteomalacia (i.e., any diseases/conditions associated with increase of phosphate). Thus, in view of this and in view of the secondary reference, one of ordinary skill in the art would understand that the phrase "treatment of various rarefying bone diseases" would include treatment of hyperphosphatemia. Therefore, given the combined teachings of the prior art, one of ordinary skill in the art would be motivated to administer orally the peptidic compound of the primary reference for the intended purpose of treating conditions associated with elevated phosphate levels (i.e., hyperphosphatemia).

With respect to repeatedly administering the peptidic composition once a day or more over a period of 30 days or more (claim 16); the reference states that the composition is administered for a prolonged period of time, wherein the prolonged period of time may be short as one day but is more preferably a period of weeks (> 7 days) or months (> 30 days) (See e.g., col. 3, lines 35-48). Thus, in view of this, one of ordinary skill in the art would understand that the duration of the administration time

depends on the condition of the individual. Hence, the duration of the administration time, dosage levels and route of administration varies depending on a number of factors including the nature of the subject to be treated (age, sex, weight, etc.), the particular nature of the condition to be treated and its severity, the particular compound used as active ingredients, the route of administration, the formulation, and the judgment of the practitioner.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated at the time the invention was made to employ a method of treating hyperphosphatemia by administering orally to an individual a therapeutically effective amount of a composition comprising a peptidic compound characterized by a) oral bioavailability, b) 4-30 amino acid residues, and c) having at least one amino acid residue which is phosphorylated or which is phosphorylatable *in vivo* or *in vitro*, and repeatedly administering the composition over a period of time, thereby reducing serum phosphate levels in the individual, absent of sufficient objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

3. The rejection of claims 12-16 and newly submitted claims 20-22 under 35 U.S.C. 103(a) as being unpatentable over Reynolds (U.S. Patent No. 5,015,628) in view of Monier-Faugere et al., (Cecil Textbook of Medicine, 21st Edition, Volume 2, Chapter 266, pages 1409-1414, edited by Goldman, Published by W.B. Saunders Company, 2000).

Applicant's arguments filed 10/17/03 have been fully considered but they are not persuasive. Applicant's arguments that the primary reference of Reynolds does not teach or disclose or suggest a method of treating hyperphosphatemia. Rather, Reynolds relates to a method of treating dental diseases such as caries, gingivitis, and periodontal diseases, rarefying boned diseases such as osteoporosis and ostiomalacia, and diseases relating to malabsorption of minerals. Further, Applicant notes that accumulation in plaque and enamel is not a reduction in serum phosphate levels. Thus, an increase in absorption of phosphate from the gut would be expected to increase serum phosphate levels, not to decrease serum phosphate levels, as presently claimed is unpersuasive. Contrary to Applicant's arguments, the prior art of Reynolds renders the claim obvious because it teaches a composition comprising a phosphopeptide having 5-30 amino acids, wherein the composition is in a form of pharmaceutical composition and administered orally to a mammal in a therapeutically effective amount (See e.g., col. 1, lines 10 to col. 2, lines 8 and col. 3, lines 9-14). The reference of Reynolds on col. 2, lines 50-68 further teaches that the composition preferably comprises a peptide which is present as 0.01 to 10% by weight which is a unit of 1 to 1000, and as such is equivalent to a composition comprising 1 to 1,000 mg of the peptide compound as claimed in claim 13 (i.e., since mg reflects weight unit). Also, the reference discloses that the peptidic compound exhibits a reduction in hydroxyapatite dissolution rate of at least 15% which meets the limitation of reduction serum phosphate levels 5% or more of claim 15 because on col. 6, lines 59-61, the reference states that

the **reduction** in hydroxyapatite dissolution was related to phosphoserine content and spacing within a peptide. This is a clear indication of decreasing of phosphate levels.

The references of Reynolds differ from claims 12-16 and 20-22 in not teaching a method of treating hyperphosphatemia (an excess amount of phosphate in the blood) by administering orally the peptidic compound claimed. However, the primary reference of Reynolds on col. 8, lines 27-34 states that the ability of these peptides to sequester calcium phosphate can be utilized in the treatment of various rarefying bone diseases. These peptides can significantly increase the absorption of calcium, phosphate and iron in the gut. Hence, pharmaceutical vehicles (e.g., enteric capsules) or foods containing calcium phosphate T1 and ferrous phosphate T1 can be used for the treatment of osteoporosis/osteomalacia and anemia. Again, contrary to Applicant's arguments this is an indication that phosphate levels decrease. Further, the secondary reference of Monier-Faugere et al., teaches the association of diseases of bone and bone mineral metabolism. For example, on page 1409, the reference teaches the relationship and/or coexistence of calcium, parathyroid hormone (PTH) and phosphate in renal osteodystrophy, which encompasses a wide variety of derangements in mineral and bone metabolism. Furthermore, on page 1410, the reference discloses the associations and mechanisms of how hyperphosphatemia result in advanced renal failure in which the increased serum phosphorus levels and PTH further decreases serum calcium through physicochemical binding affecting the histological pattern of renal osteodystrophy resulting in a profound decrease in bone turnover, i.e., low number of active remodeling sites resulting in bone resorption and suppressed bone formation.

Moreover, the primary reference of Reynolds suggests the treatment of various rarefying bone diseases such as osteoporosis/osteomalacia (i.e., any diseases/conditions associated with increase of phosphate). Thus, in view of this and in view of the secondary reference and in view of the claim language "comprising", one of ordinary skill in the art would understand that the phrase "treatment of various rarefying bone diseases" would include treatment of hyperphosphatemia. Therefore, given the combined teachings of the prior art, one of ordinary skill in the art would be motivated to administer orally the peptidic compound of the primary reference for the intended purpose of treating conditions associated with elevated phosphate levels (i.e., hyperphosphatemia).

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated at the time the invention was made to employ a method of treating hyperphosphatemia by administering orally to an individual a therapeutically effective amount of a composition comprising a peptidic compound characterized by a) oral bioavailability, b) 4-30 amino acid residues, and c) having at least one amino acid residue which is phosphorylated or which is phosphorylatable *in vivo* or *in vitro*. Thus, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the prior art teachings would have been obvious because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Betz*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but

rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

ACTION IS FINAL

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION AND FUTURE CORRESPONDENCE

5. Claims 12-16 and 20-22 are rejected and claims 1-11 and 17-19 are withdrawn as non-elected invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ROBERT A. WAX
PRIMARY EXAMINER

AAM Mohamed/AAM

January 11, 2004